IOSR Journal Of Pharmacy And Biological Sciences (IOSR-JPBS)
e-ISSN:2278-3008, p-ISSN:2319-7676. Volume 19, Issue 1 Ser. 2 (Jan. – Feb. 2024), PP 42-44
www.Iosrjournals.Org

Cidofovir-Induced Panuveitis In A Kidney Pancreatic Transplant Patient With Refractory Bk Polyomavirus Viremia

Iza Zabaneh[1], Taylor Juran[1], Tanner Dunn[2]
[1]tcu School Of Medicine, [2]unt Health Science Center

Abstract
Drug induced uveitis (DIU) is a relatively rare complication of systemic therapy, and often goes undiagnosed due to its infrequency. However, when it happens, it can carry serious ophthalmologic complications. We present a case of a patient who developed Cidofovir-induced panuveitis following its intravenous administration in the management of refractory BK polyomavirus. Prompt administration of periocular glucocorticoid therapy yielded minimal visual improvement, and the patient required subsequent Tocilizumab therapy. Despite management and resolution of the panuveitis, the patient subsequently required a keratoplasty to largely improve his vision.
Keywords*: BK polyomavirus; uveitis; glucocorticoids; Tocilizumab.*

Date of Submission: 15-02-2024 Date of Acceptance: 25-02-2024

I. Introduction

Cidofovir is an acyclic monophosphate nucleotide analog that is used to inhibit the viral DNA polymerase. It is sometimes used to treat some refractory viral infections like BK polyomavirus. We report a case of a 59 year old transplant patient who developed drug resistant polyomavirus . Treating the patient with Cidofovir was associated with a severe case of uveitis necessitating the treatment with Tocilizumab.

II. Case Report

A 59 year old gentleman with a history of kidney pancreatic transplant for diabetic nephropathy. His treatment regimen included induction with 3 doses of Thymoglobulin and Solu-Medrol. His chronic immunotherapy consisted of prednisone, Prograf, and Cellcept. On a routine 4 month post-transplant follow-up, the patient presented with some malaise, fatigue, and a low-grade fever. The workup was negative except for elevated creatinine from a baseline of 1.2 mg/dl to 1.8 mg/dl. Cytomegalovirus (CMV) titer was negative, but his BK viral load was up to 106,000 particles. In response, the patient was admitted for intravenous hydration. A kidney biopsy showed mild tubulitis with a positive BK stain and mild acute rejection with a negative presence of CD4 T-cells. Transduodenal pancreatic biopsy did not reveal any rejection.

Due to the high viral load, the prednisone dose was tapered down, Prograf tacrolimus was switched to a lower dose cyclosporine, and Cellcept therapy was discontinued. Creatinine level decreased to 1.3 mg/dl but follow-up at the clinic did not show any reduction in the viral load. Due to the concern of BK virus triggering acute transplant rejection, the patient was treated with a course of Gamunex immunoglobulin. However, this regimen had to be stopped due to side effects including nausea, vomiting and fever. The viral load went down to 7,000 but only lasted for two months with the BK levels rebounding up to 40,000 levels, alongside a slow rise in creatinine. Leflunomide, a pyrimidine synthesis inhibitor, was started. Despite the above measures, the viremia remained refractory with the continuous rise of the viral titer up to 140,000. In response, Cidofovir was started by infectious disease at 5 mg/Kg body weight intravenous injections twice weekly for 2 months decreasing the viral load to 4,000. Unfortunately, due to a continued worsening of vision , the medication was stopped. Ophthalmology evaluation showed panuveitis. Periocular steroid injections did not result in any improvement in vision. Therefore, the patient was started on Tocilizumab (Actemra) injections watching viral titer closely to avoid relapse. The uveitis eventually improved. However, due to corneal scarring, the patient required a keratoplasty which further improved his vision.

III. Discussion

Uveitis is a potentially serious ophthalmic disorder that can threaten the vision of the involved patient. It is considered an intraocular inflammatory process with numerous etiologies (infectious, idiopathic, traumatic, toxic, or chemical, genetic, parasitic, post-surgical, post-infectious, and drug-induced) that affect various structures of the eye including the uveal tract (iris, ciliary body, and choroid) and adjacent structures (cornea,

sclera, vitreous humor, and retina). While uveitis is not limited to any age group, it is most commonly observed in the third and fourth decades of life and is responsible for 2.8-10% (30,000 new cases annually) of legal blindness in the United States [1]. Uveitis presentation varies based on the anatomical site of the inflammation (anterior, intermediate, posterior uveitis, panuveitis) and etiology (infectious, non-infectious, idiopathic). Anterior uveitis is the most common presentation of uveitis with an estimated 14-17 cases per 100,000. It primarily affects the iris, anterior ciliary body, or both [2]. Anterior uveitis is most often linked to non-infectious etiologies making up approximately 80% of anterior uveitis cases. Posterior uveitis is the second most common cause of uveitis, affecting the retina or choroid. Compared to the other potential anatomical locations of uveitis, posterior uveitis most commonly has an infectious etiology. Toxoplasma gondii accounts for an estimated 40% of posterior uveitis cases between both developing and developed areas. Systemic inflammatory conditions such as systemic lupus erythematosus (SLE), sarcoidosis, and multiple sclerosis are also linked to posterior uveitis [3,4]. Intermediate uveitis affects the vitreous and pars plana . It accounts for a small portion of uveitis cases, with the majority of cases (69%) being attributed to idiopathic, non-infectious origins; however, a notable association is observed with specific diseases such as sarcoidosis accounting for a significant proportion of cases (7-18%) . Panuveitis can be diagnosed when the anterior chamber, vitreous, and retina or choroid are inflamed simultaneously. Each ocular compartment presents an equal degree of inflammation without one compartment being the predominant site of inflammation. Causes of panuveitis are more commonly idiopathic and non-infectious.

Cidofovir is an acyclic monophosphate nucleotide analog which competitively inhibits viral DNA polymerase, preventing the incorporation of deoxycytidine triphosphate (dCTP) into viral DNA, and halting viral progeny elongation and replication. In its native form, Cidofivir contains a phosphate group and therefore does not require phosphorylation in order to be activated. However, phosphorylation to its diphosphate form converts Cidofivir into its *most* active form. In vitro analysis, Cidofivir demonstrated activity against herpes virus, papillomavirus, poxvirus, polyomavirus, adenovirus, thymidine kinase negative HSV, UL97 phosphotransferases negative cytomegalovirus, and BK-virus[5]. Specifically, low dose Cidofivr has proven useful in the management of BK-virus associated cystitis in patients following organ and hematopoietic stem cell transplants [6].

Systemic medications that have been reported to be associated with drug-induced uveitis include Rifabutin, Cidofovir, Fluoroquinolone antibiotics, Bisphosphonates, BRAF kinase inhibitors (Vemurafenib and Dabrafenib), and cancer immune checkpoint inhibitors (including ipilimumab, pembrolizumab, atezolizumab, durvalumab, and nivolumab) [7] [8]. Drug induced uveitis following intravenous Cidofovir therapy has largely been studied in the management of CMV retinitis; and has been reported that following 4-11 doses of intravenous Cidofovir, 26-52% of patients developed anterior uveitis. The exact mechanism underlying the Cidofovir associated uveitis remains unclear. A direct toxicity pathogenesis has been proposed; specifically in patients who develop concurrent hypotony. Secondary hypotony has been reported to be due to direct toxic damage to the ciliary body. Additionally it has been suggested that elevations in CD4+ T lymphocyte levels may contribute to the development as well. [9]

In initial management of drug induced uveitis, often discontinuation of the offending agent provides some benefit. In addition to discontinuation, timely administration of topical/oral glucocorticoids, mydriatic/cycloplegics, and analgesics as needed. The use of glucocorticoids provides an anti-inflammatory benefit and the use of mydriatic/cycloplegics attempts to manage symptoms by embolization of the iris, decrease risk posterior synechiae and subsequent iris bombe and elevated intraocular pressures [10] [11]. Severe or refractory cases may require additional systemic glucocorticoids and/or systemic immunosuppressive agents. Given lack of improvement after initial management, this patient was started on Tocilizumab, with a significant improvement subsequently. Tocilizumab is a humanized monoclonal antibody IL-6 receptor antagonist and has been studied more extensively within pediatric populations in the management of uveitis secondary associated with refractory juvenile idiopathic arthritis that is refractory to anti-TNF agents. In adult patients with resistant noninfectious uveitis, it is theorized that Tocilzumab may provide some benefit; particularly if there is CME present [12] [13]. Complications of prolonged untreated uveitis can include secondary cataracts, posterior synechiae, ERM, band keratopathy, hypotony, secondary glaucoma, uveitic glaucoma, papilledema. Additionally, the utilization of topical and systemic glucocorticoids for prolonged periods can result in elevated intraocular pressure; subsequently increasing the risk for secondary glaucoma. Despite treatment and good response to Tocilzumab, the patient did develop corneal scarring, which subsequently required keratoplasty to improve vision [14].

IV. Conclusion

The presented case study strongly suggests that uveitis is a frequent and alarming side-effect of intravenous Cidofovir use. While Cidofovir is an antiviral used to treat common viral infections, including those affecting the eyes, healthcare professionals must proceed with caution when considering Cidofovir for ocular use. Therefore, when managing ocular viral infections with Cidofovir, we recommend close monitoring of patients,

including but not limited to regular eye examinations, renal and liver function tests, blood cell count, and viral load testing (especially in the context of CMV and HIV).

References

[1]. Foster, C. Stephen, And Albert T. Vitale. Diagnosis & Treatment Of Uveitis. Jp Medical Ltd, 2013.
[2]. Harthan Js, Opitz Dl, Fromstein Sr, Morettin Ce. Diagnosis And Treatment Of Anterior Uveitis: Optometric Management. Clin Optom (Auckl). 2016 Mar 31;8:23-35.
[3]. Andrea York Tiang Teo , Bjorn Kaijun Betzler , Keith Low Qie Hua , Elizabeth Jiahui Chen , Vishali Gupta & Rupesh Agrawal (2023) Intermediate Uveitis: A Review, Ocular Immunology And Inflammation, 31:5, 1041-1060.[
[4]. Giorgiutti S, Jacquot R, El Jammal T, Bert A, Jamilloux Y, Kodjikian L, Sève P. Sarcoidosis-Related Uveitis: A Review. J Clin Med. 2023 Apr 29;12(9):3194.
[5]. Clercq Ed. Clinical Potential Of The Acyclic Nucleoside Phosphonates Cidofovir, Adefovir, And Tenofovir In Treatment Of Dna Virus And Retrovirus Infections. Clin Microbiol Rev. 2003 Oct; 16(4): 569–596.
[6]. Savona, M., Newton, D., Frame, D. Et Al. Low-Dose Cidofovir Treatment Of Bk Virus-Associated Hemorrhagic Cystitis In Recipients Of Hematopoietic Stem Cell Transplant. Bone Marrow Transplant 39, 783–787 (2007).
[7]. Agarwal M, Majumder Pd, Babu K. Drug Induced Uveitis: A Review. Indian J Ophthalmology. 2020 Sep; 68(9): 1799–1807. Published Online 2020 Aug 20.
[8]. Dow Er, Yung M, Tsui E. Immune Checkpoint Inhibitor-Associated Uveitis: Review Of Treatments And Outcomes. Ocul Immunol Inflamm. 2021 Jan 2;29(1):203-211.
[9]. Akler Me, Johnson Dw, Burman Wj, Johnson Sc. Anterior Uveitis And Hypotony After Intravenous Cidofovir For The Treatment Of Cytomegalovirus Retinitis. Ophthalmology 105(4): 651-7, 1998
[10]. Agrawal Rv, Murthy S, Sangwan V, Biswas J. Current Approach In Diagnosis And Management Of Anterior Uveitis. Indian J Opthalmol. 2010 Jan-Feb; 58(1): 11–19.
[11]. Babu K, Mahendradas P. Medical Management Of Uveitis - Current Trends. Indian J Opthalmol. 2013 Jun; 61(6): 277–283.
[12]. Lo Tc, Rogers S, Ross, L. Tocilzumab In Adult Non Infectous Uveitis. Investigative Ophthamology & Visual Science. 2023 June, Vol 2023;64(8):3569.
[13]. Sepah, Yj. Sadiq Ma, Chu Ds. Primary (Month-6) Outcomes Of Stop-Uveitis Study: Evaluating The Safety, Tolerability, And Efficacy Of Tocilizumab In Patients With Noninfectious Uveitis. American Journal Of Ophthalmology. 2017 September, Vol 183, P71-80.
[14]. Duplechain A, Conrady C, Patel B. Uveitis. [Updated 2023 Aug 8]. In: Statpearls [Internet]. Treasure Island (Fl): Statpearls Publishing; 2024 Jan-.